Remarks

Amendments to the Claims

Independent claims 1, 7, and 13 are amended to recite an "antisense oligonucleotide which is complementary to mRNA encoding PSD95," which is supported *inter alia* by canceled dependent claims 3, 9, and 15.

Claims 5, 11, and 17 are amended to recite "nucleotides 241 to 258 of PSD95," which conforms to claim 22 and is supported on page 6, line 17.

New claims 66-68 recite that the subject is a human and are supported in the specification on page 7, lines 14-16: "Preferably the formulations of the invention will be manufactured under regulatory-approved conditions for administration to humans."

The amendments add no new matter.

Priority

Applicants have corrected the typographical error in the priority application's serial number.

Objections to the Claims

Claims 1, 7, 13, 19, 45-61, and 65 are objected to because they recite non-elected subject matter. Claims 45-61 and 65 have been canceled. Claims 1, 7, 13, and 19 have been amended to delete the non-elected subject matter (PSD93).

Please withdraw the objection.

Rejections Under 35 U.S.C. § 112 ¶ 2

Claims 4, 10, 16, and 21 stand rejected under 35 U.S.C. § 112 ¶ 2 as indefinite. Applicants respectfully traverse the rejection.

Dependent claims 4, 10, and 16 recite "the antisense oligonucleotide," which the Office Action asserts has insufficient antecedent basis. The independent claims from which claims 4, 10, and 16 depend (claims 1, 7, and 13, respectively) have been amended to recite "an antisense oligonucleotide," which provides antecedent basis.

Claim 21 is rejected as indefinite because it recites "C-terminal PDZ domain" and the carboxy-terminal portion of PSD95 contains a guanylate kinase domain. Claim 21 has been amended to delete the term "C-terminal."

Please withdraw the rejections.

Rejection Under 35 U.S.C. § 112 ¶ 1 (written description)

Claims 1, 3-7, 9-13, 15-22, 24, 25, 34, 62, and 64 stand rejected under 35 U.S.C. § 112 ¶ 1 as insufficiently described. Applicants respectfully traverse the rejection.

The first paragraph of 35 U.S.C. § 112 requires that the specification "contain a written description of the invention." The purpose of the written description requirement is to assure that an applicant was in possession of the claimed subject matter on the date the application was filed. *Vas-Cath Inc. v. Mahurkur*, 19 U.S.P.Q.2d 1111, 1116-17 (Fed. Cir. 1991).

The specification must be considered from the viewpoint of a skilled artisan at the priority date of the application. *In re Wertheim*, 541 F. 2d 257, 262, 191 U.S.P.Q. 90, 96 (C.C.P.A. 1976). A specification adequately describes a genus to the skilled artisan if it permits the artisan to "visualize or recognize members of the genus." *University of California v. Eli Lilly*

and Co., 119 F.3d 1559, 1568, 43 U.S.P.Q.2d 1398, 1406 (Fed. Cir. 1997). The present specification meets this criterion.

Most of the rejection is based on the breadth of the term "agent" in the method claims: the Office Action contends that the specification does not sufficiently describe the "expansive genus of structurally distinct compositions capable of inhibiting the expression of all known, and unknown, PSD95 genes encoded by all metazoans." Office Action at page 4, ¶ 3. To advance prosecution, method claims 1, 3-7, 9-13, 15-18, 34, 62, and 64 now recite "an antisense oligonucleotide which is complementary to mRNA encoding PSD95" rather than "an agent." Composition claims 19-22, 24, and 25 as originally filed each recited "an isolated and purified antisense polynucleotide which is complementary to PSD95 mRNA." Recitation in the claims of "antisense oligonucleotide" moots those portions of the rejection based on the breadth of the genus "agent."

The Office Action also contends that the specification's disclosure of an antisense oligonucleotide which is complementary to nucleotides 241-358 of the rat PSD95 nucleotide sequence (GenBank Accession No. M96853) does not sufficiently represent the recited genus of antisense oligonucleotides because "the specification does not provide any disclosure whether these sequences from other species would have had the same characteristics or would have had additional characteristics or properties." Page 5, ¶ 1. In fact, the PSD95 mRNA of M96853 (rat) is highly representative of other PSD95 mRNAs. It is, for example, 96% identical to the mouse PSD95 mRNA, 94% identical to the dog PSD95 mRNA, and 93% identical to each of the human, the macaque, and the chimp PSD95 mRNAs. See the BLAST alignment which accompanies this response. The Office Action does not set forth any express findings of fact as

to why antisense oligonucleotides which inhibit expression of rat PSD95 would not also inhibit expression of the highly similar PSD95 mRNAs from other species.

Finally, the Office Action faults the specification because it does not disclose "identifying characteristics" of various delivery vehicles for the antisense oligonucleotides (*e.g.*, a plasmid vector, liposome, virus particle, "or some other protective formulation"). Paragraph bridging pages 5 and 6 of the Office Action. It is well-established that "[t]he description need only describe in detail that which is new or not conventional in the art." M.P.E.P. § 2163(II)(A)(3)(a), citing *Hybritech v. Monoclonal Antibodies*, 802 F.2d 1367, 1384, 231 U.S.P.Q. 81, 94 (Fed. Cir. 1986). *See also* the U.S. Patent and Trademark Office's own Revised Interim Written Description Guidelines Training Materials at page 4:

> It is assumed at this point in the analysis that the specification has been reviewed and an appropriate search of the claimed subject matter has been conducted. It is also assumed that the examiner has identified which features of the claimed invention are conventional taking into account the body of existing prior art.

The specification need not describe "identifying characteristics" of delivery vehicles for antisense oligonucleotides because such vehicles and their use were within the knowledge of the skilled artisan when the application was filed. *See*, *e.g.*, col. 20, line 19 to col. 24, line 67 and col. 25, line 1 to col. 28, line 33 of U.S. Patent 5,877,309. A specification need not teach, and preferably omits, what is well known in the art. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 U.S.P.Q. 81, 94 (Fed. Cir. 1986).

The present specification, together with the knowledge in the relevant field, adequately describes the subject matter of claims 1, 3-7, 9-13, 15-22, 24, 25, 34, 62, and 64. Please withdraw the rejection.

Rejection Under 35 U.S.C. § 112 ¶ 1 (enablement)

Claims 1, 3-7, 9-13, 15-22, 24, 25, 34, 62, and 64 stand rejected under 35 U.S.C. § 112 ¶ 1 as not enabled for their full scope. Applicants respectfully traverse the rejection.

The enablement requirement of 35 U.S.C. § 112 ¶ 1 states that a patent specification must teach a person skilled in the relevant art how to make and use the invention claimed. Whether a specification enables a claimed invention is a question of law based on underlying factual findings. *In re Vaeck*, 947 F.2d 488, 495, 20 U.S.P.Q.2d 1438, 1444 (Fed. Cir. 1991). The proper standard for determining whether the present specification meets the enablement requirement is whether any experimentation which may be needed to practice the methods of claims 19, 23-25, 30-46, and 49-57 is undue or unreasonable. *In re Wands*, 858 F.2d 731, 736-37, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988).

The U.S. Patent and Trademark Office has the initial burden to establish a reasonable basis to question the specification's enablement of the claims. *In re Wright*, 999 F.2d 1557, 1562, 27 U.S.P.Q.2d 1510, 1513 (Fed. Cir. 1993). To make a *prima facie* case of non-enablement using this standard, an Examiner must properly construe the claims and must weigh all the evidence and establish a reasonable basis to question the enablement provided in the specification for the claimed invention. M.P.E.P. §§ 2164.04 and 2164.05, 8th ed., revised August, 2006.

On pages 8-9 the Office Action sets forth a list of aspects of the claimed methods and compositions which it asserts the specification does not enable. Each is addressed in turn.

"enormous genus of agents"

Portions of the rejection based on the "enormous genus of agents" are moot because the claims all recite antisense oligonucleotides, rather than "agent."

"enormous genus of antisense oligonucleotides complementary to an enormous genus of nucleotides encoding a PDZ domain"

The Office Action contends that the specification does not enable the "enormous genus of antisense oligonucleotides complementary to an enormous genus of nucleotides encoding a PDZ domain" because, for example, "over 394 different PDZ domains have been found in humans." Paragraph bridging pages 10 and 11. The claims do not recite a genus this broad. All the antisense oligonucleotides recited in the pending claims must be "complementary to mRNA encoding PSD95."

"enormous genus of antisense oligonucleotides complementary to an enormous genus of nucleotides encoding an enormous genus of PSD95 messenger RNAs"

"enormous genus of antisense oligonucleotides complementary to nucleotides encoding an enormous genus of carboxy-terminal PDZ domains of an enormous genus of PSD95 proteins"

The Office Action provides no basis for its assertion that either the genus of PSD95 mRNAs or the genus of PDZ domains of the mRNAs is "enormous." In fact, as noted above in connection with the written description rejection, PSD95 coding sequences are highly homologous to each other, and the rat PSD95 sequence disclosed in the application is representative. Neither the genus of PSD95 mRNA nor the genus of PDZ domains contained with PSD95 mRNA is "enormous."

"enormous genus of means or routes of administration of the pharmaceutical composition(s)"

"enormous genus of anesthetics"

"enormous genus of carriers for an enormous genus of agents"

A specification need not teach, and preferably omits, what is well known in the art. *Hybritech*, 231 U.S.P.Q. at 94. The specification teaches the following routes of administration: intrathecal, *per os*, intravenous, subdermal, subcutaneous, rectal, intraperitoneal, subarachnoid, caudal, epidural, inhalation, and intramuscular. Page 6, last ¶. Each of these methods is well known in the art. For example, routes of administering antisense oligonucleotides are described in detail in U.S. Patent 5,877,309 (*see* col. 25, line 1 to col. 28, line 33).

Anesthetics and methods of administering them also are well known and are taught in a variety of textbooks which were available long before the priority date of this application. These textbooks include Barash *et al.*, eds., Clinical Anesthesia, 2d ed., 1992; Barash *et al.*, Handbook of Clinical Anesthesia, 2d ed., 1993; Collins, Principles of Anesthesiology: General and Regional Anesthesia, 3d ed., 1993; Cote *et al.*, A Practice of anesthesia for Infants and Children, 2d ed., 1993; Longnecker & Murphy, Dripps/Eckenhoff/Vandam Introduction to Anesthesia, 8th ed., 1992; Miller, Anesthesia, 4th ed., 1994; Morgan & Mikhail, Clinical Anesthesiology, 2d ed., 1995; Rogers *et al.*, Principles and Practice of Anesthesiology, 1993; Saidman & Smith, Monitoring in Anesthesia, 3d ed., 1993; Stoelting & Dierdorf, Anesthesia and Co-Existing Disease, 3d ed., 1993.

Finally, carriers which can be used with antisense oligonucleotides in particular (rather than with "agents," which the claims no longer recite) are well known. *See, e.g.*, U.S. Patent 5,877,309 at col. 20, line 19 to col. 24, line 67.

Neither the routes of administration, the genus of anesthetics, or carriers for the oligonucleotide compositions requires any additional enablement beyond what is practiced in the art.

"enormous genus of subjects"

"Subject" as recited in claims is not an "enormous genus" as the Office Action asserts, but is limited by other recitations in the claims. All the recited subjects must express mRNA encoding PSD95. In addition, the subject recited in claims 1 and 4-6 must have "acute or chronic pain"; the subject recited in claims 7 and 11-12 must have or be prone to develop hyperalgesia. The subject recited in claims 13 and 16-18 must be one to which anesthesia is administered. In addition, the subject of claims 6, 12, and 18 must be a subject to which the oligonucleotide can be administered intrathecally (*i.e.*, the subject has a spine or a brain, which eliminates numerous metazoans). "Subject," therefore, does not encompass "all metazoan subjects," as the Office Action on page 10 ¶ 1 asserts.

"method for preventing hyperalgesia"

At pages 11 and 12, the Office Action cites several publications (Chirila,[1] Jen,[2] and Stein[3]) to support its contention that administration of oligonucleotides for therapeutic purposes is unpredictable. Neither of the three references is persuasive.

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[1] Chirila *et al.*, "The use of synthetic polymers for delivery of therapeutic antisense oligodeoxynucleotides," *Biomaterials 23*, 321-42, 2002.

[2] Jen & Gewirtz, "Suppression of Gene Expression by Targeted Disruption of Messenger RNA: Available Options and Current Strategies," *Stem Cells 18*, 307-19, 2000.

[3] Stein, "Is irrelevant cleavage the price of antisense efficacy?" *Pharmacol. Therapeutics 85*, 231-36, 2000.

Chirila addresses the use of synthetic polymers as carrier matrices and/or cell membrane permeabilization agents for delivery of antisense oligonucleotides, which is but one way to deliver oligonucleotides. Jen discusses various aspects of gene targeting. Stein discusses scission of non-targeted mRNAs. All three references acknowledge that antisense therapy is not perfected in all aspects. Perfection, however, is not what is required for enablement. In fact, by the May 12, 2000 priority date of this application, numerous clinical trials using a variety of antisense oligonucleotides had been carried out and reported in the literature. The following list is a sampling:[4]

- Chen *et al.*, *Clin. Cancer Research 6*, 1259-66, April 2000 (antisense oligonucleotide targeting type I protein kinase A);
- Stevenson *et al.*, *J. Clin. Oncol. 17*, 2227-36, July 1999; O'Dwyer *et al.*, *Clin. Cancer Res. 5*, 3977-82, December 1999; Cunningham *et al.*, *Clin. Cancer Res. 6*, 1626-31, May 2000 (antisense oligonucleotide targeting c-*raf*-1);
- de Smet *et al.*, *Ocul. Immunol. Inflamm. 7*, 189-98, December 1999 (antisense oligonucleotide for treating CMV retinitis);
- Nemunaitis *et al.*, *J. Clin. Oncol. 17*, 3586-95, November 1999 and Yuen *et al.*, *Clin. Cancer Res. 5*, 3357-63, November 1999 (antisense oligonucleotide targeting protein kinase C-α);
- Clark *et al.*, *Bone Marrow Transplantation 23*, 1303-08, 1999 (antisense oligonucleotide targeting the breakpoint in *BCR-ABL* mRNA);
- Gewirtz, *Oncogene 18*, 3056-62, May 13, 1999 (antisense oligonucleotide targeting the *myb* gene);
- Sereni *et al.*, *J. Clin. Pharmacol 39*, 47-54, January 1999 (antisense oligonucleotide targeting HIV *gag*);
- Glover *et al.*, *J. Pharmacol. Exptl. Ther. 282*, 1173-80, 1997 (antisense oligonucleotide targeting ICAM-1); and

[4] Copies of the cited documents are provided with the accompanying IDS.

- Waters *et al.*, *J. Clin. Oncol. 18*, 1812-23, May 2000 (antisense oligonucleotide targeting *Bcl-2*).

In contrast to the academic cautions of Chirila, Jen, and Stein, those skilled in the art clearly had extensive practical experience in antisense oligonucleotide therapy by the priority date of this application.

It is hornbook law that "the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art." *In re Fisher*, 427 F.2d 833, 839, 166 U.S.P.Q. 18, 24 (C.C.P.A. 1970). The specification enables the full scope of properly construed claims 1, 3-7, 9-13, 15-22, 24, 25, 34, 62, and 64 and of new claims 66-68. Please withdraw the rejection.

Respectfully submitted,
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